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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/196,161	11/20/1998	YOKE MIN SIN	1459-005B	8822

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EXAMINER
MINNIFIELD, NITA M

ART UNIT	PAPER NUMBER
1645	46

DATE MAILED: 04/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

4)

S-M

Office Action Summary	Application No. 09/196,161	Applicant(s) SIN ET AL.	
	Examiner N. M. Minnifield	Art Unit 1645	

-- Th MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

1. Applicants' Response filed January 31, 2003 is acknowledged and has been entered. Claims 1-8 are now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment with the exception of those discussed below.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 1, 3, 4 and 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Lin et al (Dev. Biol. Stand. 1997, 90:461). Library of Congress stamped date is August 21, 1997.

The claims are directed to a vaccine comprising a recombinant fusion protein, GST-iAgI, and substantially inert medium (buffer, adjuvant, immunostimulant, or carrier).

Lin et al disclose a recombinant protein, I-antigens as candidates for a recombinant subunit vaccine and indicate that the route of administration may be crucial for the development of a protective antibody response (abstract). Lin et al disclose that "fish surviving infection with the parasitic ciliate *I. multifiliis* are resistant to subsequent challenge suggesting that vaccination is possible." (abstract). Lin et al disclose that "...abundant surface membrane proteins (referred to as immobilization antigens, or I-ags) whose role in eliciting a

protective response is indicated by the fact that immune fish produce parasite-immobilizing antibodies in cutaneous mucus and sera..." (abstract). Fish immunized with the i-ag had a survival rate of 25% whereas killed whole cells or crude parasite lysates did not stimulate protective immunity (abstract).

It is noted that the prior art does not specifically recite a substantially inert medium (buffer, adjuvant, immunostimulant, or carrier). However, it would be inherent that a vaccine composition would comprise a buffer, adjuvant or carrier of some kind.

Further, the prior art does not specifically recite a recombinant fusion protein; but a recombinant protein is a fusion protein. The prior art anticipates the claimed invention.

Since the Patent Office does not have the facilities for examining and comparing applicants' vaccine with the vaccine of the prior art reference, the burden is upon applicants to show a distinction between the material structural and functional characteristics of the claimed vaccine and the vaccine of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

This rejection is maintained for the reasons of record. Applicant's arguments filed January 31, 2003 have been fully considered but they are not persuasive. Applicants have asserted that the Lin et al reference does not disclose the claimed material, a recombinant fusion protein derived from an artificial DNA sequence for immobilization antigen, repeat I of Ich. Applicants also assert that the art does not relate to the artificial DNA sequences.

However, the phrase "derived from an artificial DNA..." is viewed as a process limitation. The prior art discloses the recombinant protein as claimed. Further, as previously stated, a recombinant protein is a fusion protein. The prior art discloses the claimed composition, absent any convincing evidence to the contrary.

4. Claims 2 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al (1997) as applied to claims 1, 3, 4 and 6-8 above, and further in view of Clark et al (PNAS, 1992, 89:6363-6367) and Smith et al (Gene, 1998, 67:31-40).

Lin et al teaches a recombinant protein, I-antigens as candidates for a recombinant subunit vaccine and indicate that the route of administration may be crucial for the development of a protective antibody response (abstract). Lin et al teaches that "fish surviving infection with the parasitic ciliate *I. multifiliis* are resistant to subsequent challenge suggesting that vaccination is possible." (abstract). Lin et al teaches that "...abundant surface membrane proteins (referred to as immobilization antigens, or I-ags) whose role in eliciting a protective response is indicated by the fact that immune fish produce parasite-immobilizing antibodies in cutaneous mucus and sera..." (abstract). Fish immunized with the i-ag had a survival rate of 25% whereas killed whole cells or crude parasite lysates did not stimulate protective immunity (abstract).

It is noted that the prior art does not specifically recite a substantially inert medium (buffer, adjuvant, immunostimulant, or carrier). However, it would be inherent that a vaccine composition would comprise a buffer, adjuvant or carrier of some kind.

Further, the prior art does not specifically recites recombinant fusion protein; but a recombinant protein is a fusion protein.

Lin et al teach the claimed invention except for the specific fusion protein GST-iAg and that the fusion protein is produced in *E. coli*.

However, Clark et al teaches the expression of the immobilization antigen (i.e. i-ag); the cDNA encode a protein of 394 amino acids with a tandemly repeated structure characteristic of the i-antigen of other ciliated parasites (abstract). Clark et al teaches that the immobilization antigens of *I. multifiliis* are analogous to free-living ciliates and parasitic protozoa; and "...that transcript levels increase in parallel with the infectivity of the organism bears on the functional role in this system and is consistent with previous observations suggesting that the i-antigens of *Ich* are involved in the development of protective immunity in fish. (p. 6363, col. 2; see also p. 6367, col. 2). The materials and methods teach how to obtain a recombinant immobilization antigen (p. 6363-6365).

Smith et al teach how to make and purify fusion proteins (foreign protein with GST) that have been produced in *E. coli*. (abstract; p. 38, col. 1). Smith et al teach that expression and purification of parasitic antigens (p. 33, col. 20). Smith et al teach that using GST and *E. coli* provide a better recombinant fusion protein because it avoids the difficulties of denaturing reagents altering the antigenicity and functional activity of the purified product and immunological analysis (p. 32, col. 1).

In view of the combination of references (Lin et al, Clark et al and Smith et al) it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the methods of making recombinant fusion protein

(GST-iAgI) using *E. coli* to produce the recombinant fusion proteins with the reasonable expectation of success of making a vaccine comprising a recombinant fusion protein, GST-iAgI, and substantially inert medium. Lin et al teach that the antigen could be a recombinant subunit vaccine. Clark et al teach that other parasitic immobilization antigens are similar and Smith et al suggest and teach making recombinant fusion proteins (GST and a parasitic protein) and that they can be produced in E. coli, the same as Applicants. It would have been obvious to a person of ordinary skill in the art at the time the invention was made at to use the vaccine of Lin et al comprising the recombinant protein iAgI and adjuvant with a reasonable expectation of protecting against infection of other taxonomically related ciliated protozoan as set forth in Clark et al. Clark et al teach that other taxonomically related ciliated protozoan have the I-antigen (immobilization antigens). The claimed invention is prima facie obvious in view of the prior art absent any convincing evidence to the contrary.

The rejection is maintained for the reasons of record. Applicant's arguments filed January 31, 2003 have been fully considered but they are not persuasive. Applicants have asserted that Clark et al does not disclose artificial DNA sequences or fusion proteins derived therefrom. It is noted that this rejection is a 103 obviousness rejection in view of three references (Lin et al in view of Clark et al and Smith et al). In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re*

Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The prior art in combination as described above teaches the claimed invention. It is noted that Clark et al teaches the DNA and amino acid sequence of the immobilization antigen of Ich. Further, Applicants' claims do not recite the specific DNA sequence. It would appear that the DNA sequence and the artificial DNA sequence would be the same, since both produce recombinant proteins of the immobilization antigen of Ich. Applicants have not shown any evidence that the artificial DNA sequence would produce a better immobilization antigen for a vaccine composition for immunizing fish against ciliated ectoparasitic protozoans or any other superior or unexpected results with regard to the claimed invention.

5. No claims are allowed.

6. The information disclosure statement filed February 23, 1999 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

It is noted that the copies of all of the cited references were not available to the Examiner. Please provide all cited references on the Form 1449 if Applicants desire to have them cited on an issued patent. References not initialed were not available to the Examiner.

Applicants indicated (January 31, 2003 Response, p. 2) that copies of additional references will be supplied shortly. However, these references have not yet been received for Examiner review.

7. The references cited or used as prior art in support of one or more rejections in the instant Office Action have been previously cited on PTO-892 mailed to Applicants on December 11, 2001 and will not be mailed again.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 703-305-3394. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 703-308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

N. M. Minnifield
Primary Examiner
Art Unit 1645

Nmm
April 11, 2003